REMARKS

1. Status of the Application

Claims 1, 3-16 and 18 are pending in the present application.

Claim 18 has been amended to depend from pending Claim 16 instead of from cancelled Claim 17.

Claims 19-21 have been added to describe preferred embodiments of the instant invention. Support for each of Claims 19-21 is found in the Specification, page 38, lines 1-14, which teaches that "As indicated in Table 3, the incorporation of 6% PEG-8000 significantly and substantially enhanced the luminescent signal from the CHO-Rluc cells, in response to added bTSH . . ."

Applicant notes, with appreciation, that the Examiner withdrew the prior rejection of Claims 1 and 10-18 under 35 U.S.C. §112, second paragraph, for alleged indefiniteness

2. Rejection Of Claims 1, 3-16 and 3-18 Under 35 U.S.C. §103 Over Evans *et al.* In View Of Yamashiro *et al.*

Claims 1, 3-16 and 18 continue to be rejected under 35 U.S.C. §103 for alleged obviousness over Evans *et al.*[1] in view of Yamashiro *et al.*[2] Applicant respectfully traverses.

Applicant incorporates his prior arguments and evidence that were presented in the Amendment mailed on 2/21/02 with respect to the lack of motivation to combine the references, as well as a lack of reasonable expectation of success in practicing the claimed methods.

In addition, Applicant submits the enclosed Declaration by Dr. Leonard Kohn and its accompanying references in further support of a lack of a reasonable expectation of success in practicing the claimed invention. In particular, Dr. Kohn's factually supported Declaration teaches that (a) intracellular signal transduction is cell specific and stage specific as evidenced by Dumont *et al.*, (b) the intracellular signalling pathway(s) induced by binding of a ligand to

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[1] Evans et al. (1999) "Development of a luminescent bioassay for thyroid stimulating antibodies," J. Clin. Endocrin. Metabolism 84(1)374-377.

[2] Yamashiro et al. (1999) "Mechanism of the Augmentative Effect of High Polyethylene Glycol (PEG) Concentrations on the Thyroid Stimulating Activity in TSAb-IgG Using a Porcine Thyroid Cell Assay," Endocrine Research 25:67-75.

the TSH receptor is unpredictable even in the same cell type when obtained from different animals as evidenced by Kimura *et al.*, (c) the intracellular signalling pathway induced by binding of a ligand to the TSH receptor is unpredictable even in the same cell type when at different stages of differentiation as evidenced by Bell *et al.*, (d) the intracellular signalling pathway induced by binding of different ligands to the TSH receptor is unpredictable even in the same cell as evidenced by Yamashiro *et al.*, (e) the mechanism of action of PEG on cAMP is unknown, as evidenced by Yamashiro *et al.*, and therefore PEG's effect on cAMP in different cells is unpredictable, and (f) cAMP-signalled gene expression is unpredictable in different cells as evidenced by Kimura *et al.*, Kohn *et al.*, Damante & Di Lauro, and by Czech.[3] Based on the above, Dr. Kohn concludes that it is his:

> "opinion that one of ordinary skill in the art would not have a reasonable expectation of success that the recited CHO-Rluc cells will respond to the recited exposure to TS antibody and PEG similarly to the response of Yamashiro *et al.*'s porcine cells to TS antibody and PEG."[4]

Since Dr. Kohn is one of skill in the art,[5] his factually-based opinion rebuts a reasonable expectation of success in practicing the claimed methods.

With respect to the newly added Claims 19-21, these claims are non-obvious over the cited references for the additional reasons that Yamashiro *et al.* discloses "that the increase in cAMP production by PEG was specific for TSAb as **no stimulation** was observed by other thyroid stimulators such as **TSH**."[6] In stark contrast, new Claims 19-21 recite the **diametrically opposite** response of **stimulation by bTSH** of luciferase, which is expressed under the control of a cAMP responsive element in the recited CHO-Rluc cells.

In view of the above, it is respectfully requested that the rejection of the claims under 35 U.S.C. § 103 be withdrawn.

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[3] Dr. Kohn's Declaration, item 4.

[4] Dr. Kohn's Declaration, item 5.

[5] Dr. Kohn's Declaration, item 1; and its accompanying Curriculum Vitae at Tab 1.

[6] Yamashiro *et al.*, page 71, last paragraph.

3. Conclusion

All grounds of rejection and objection of the Office Action of June 3, 2002 having been addressed, reconsideration of the application is respectfully requested. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to **call the undersigned collect before beginning to draft a written communication**, if any.

Signed on behalf of:

Dated: December 3, 2002

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APPENDIX I

MARKED-UP VERSION OF REWRITTEN, ADDED, AND/OR CANCELLED CLAIMS

Brackets denote cancellation and underlining denotes insertion.

Amend Claim 18 and add the following new Claims 19-21.

18. (Once Amended) The method of Claim [17] 16, wherein said observing further comprises measuring the cyclic adenosine monophosphate concentration.

19. (New) The method of Claim 1, wherein luciferase activity in said CHO-Rluc cells exposed to bovine thyroid stimulating hormone is higher in the presence of polyethylene glycol than in the absence of said polyethylene glycol.

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20. (New) The method of Claim 10, wherein luciferase activity in said CHO-Rluc cells exposed to bovine thyroid stimulating hormone is higher in the presence of polyethylene glycol than in the absence of said polyethylene glycol.

21. (New) The method of Claim 16, wherein luciferase activity in said CHO-Rluc cells exposed to bovine thyroid stimulating hormone is higher in the presence of polyethylene glycol than in the absence of said polyethylene glycol.